Impact of Formulation and Process Variations on the Quality of Freeze Dried Products: How do we identify, control, and characterize critical variations?

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Some Quality Attributes for Freeze Drying- not all Critical

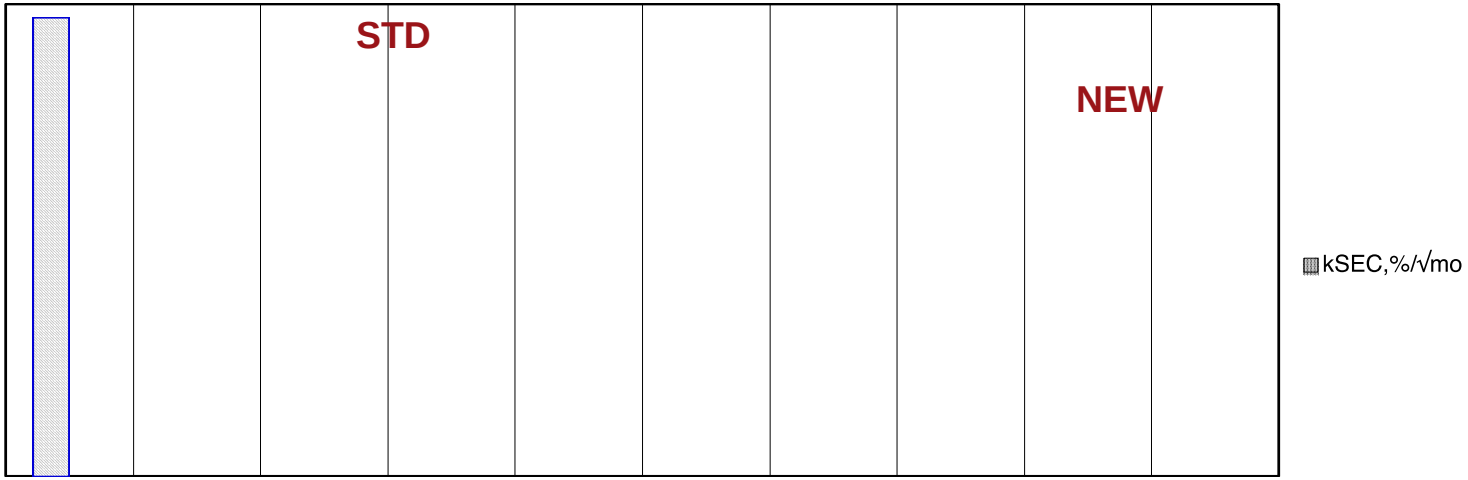
- **Sterility-critical**
- **Low endotoxin-critical**
- **Stability-critical***
  - **adequate potency**
  - **absence of toxic degradation products**
- **Rapid and easy reconstitution**
- **Cost effective process (i.e., fast)**
- **Fast development process (speed to market)**
- **"Elegance"- "beauty is in the eye of the beholder"**

- **Note: some are impacted by formulation, some by process, and many by both formulation & process**

Storage Stability is Very Sensitive to Formulation

Human Growth Hormone Formulations

Rate Constants, k(√t), at 40C (40 C << Tg)



*** all formulations except Gly:Mann are glassy**

**** Trend is same for both chemical degradation and aggregation!**

Significance of Results

- **Standard, "Current most used" commercial formulation**
  - **≈ 3% aggregation in 2 yrs at Refrigerated Storage *(estimated from literature data)***
- **Simple Sucrose Based Formulation**
  - **≈3000 years to form 3% aggregate at 25 C° *(estimated from literature data)***

- **Formulation Does Matter!**

Control of Stability by Process Control

Use "Good Freeze Drying Practice" to guide control

- **Freezing-convert water to ice**
  - **Control by control of ice nucleation temperature**
    - **Stability implications**
- **Primary Drying-sublime the ice**
  - **Control Product Temperature History**
    - **You freeze dry the product, not the shelf! (Felix Franks)**
    - **"Possible" stability implications**
- **Secondary Drying-remove non-freezable water**
  - **Control Product Temperature**
    - **Stability implications**

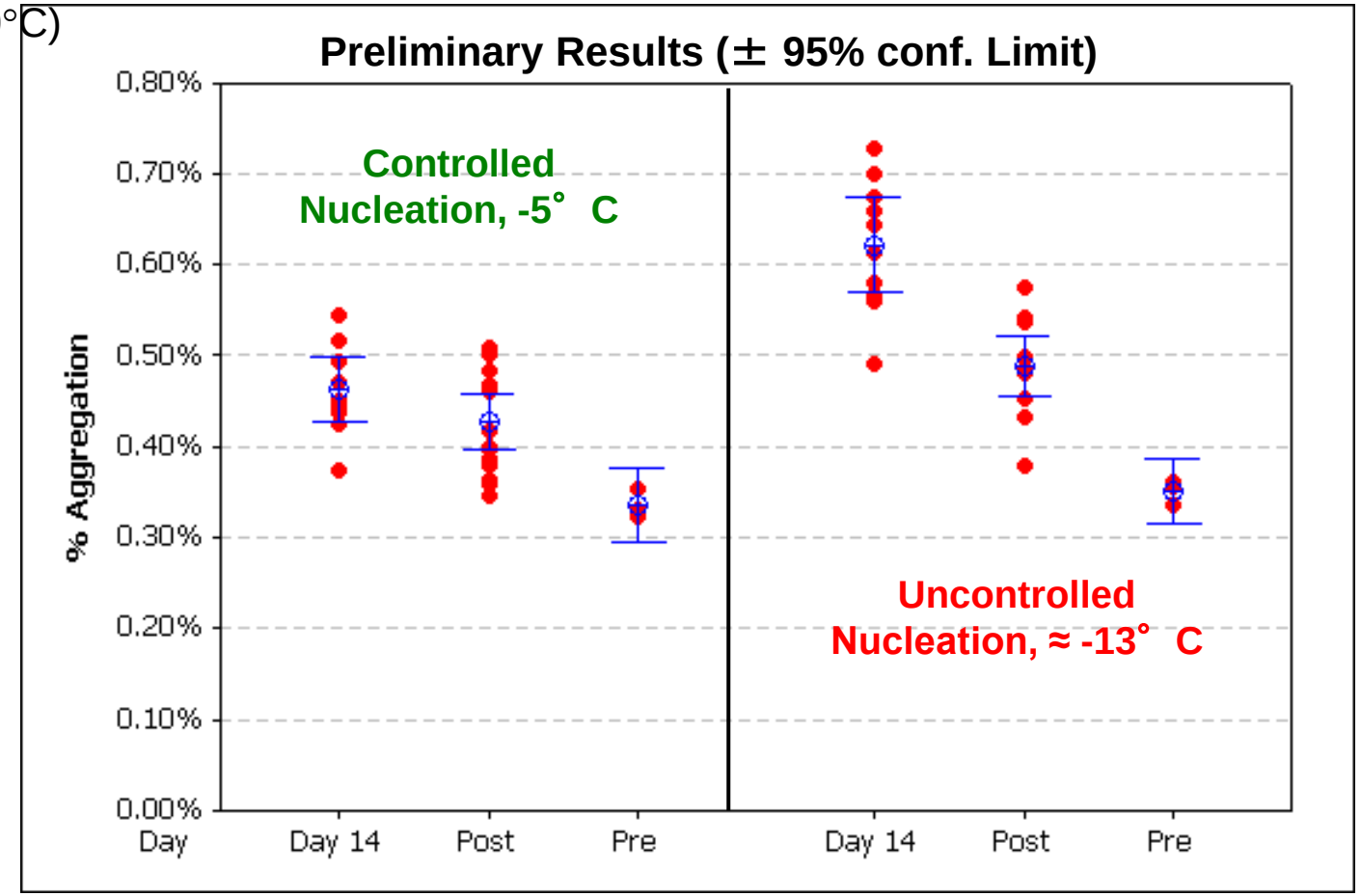
Control of Freezing

- **Conventional freezing is uncontrolled**
  - **Variable ice nucleation temperature**
    - **Development to production, intra- and inter-batch**
    - **Variable ice surface area means variable drying time and (potentially) variable stability**
      - **High surface area means potential for protein aggregation.**
- **Solution: Controlled Ice Nucleation**
  - **At least two commercial versions available for both manufacturing and development**
    - **Nucleate at moderate super-cooling (low surface area)**
    - **Same process for development as in manufacturing**

hGH Aggregation Study

Compare Stability "in-process" and "in storage" for conventional uncontrolled nucleation and controlled nucleation

- **Experiments**
  - 2 mg/mL hGH + 2 mM sodium phosphate + 6 mg/mL sucrose
  - Assay hGH aggregation via HPLC (pre- & post-freeze drying and after 14 days at 50°C)



Examine Variance by Propagation of Errors[#]

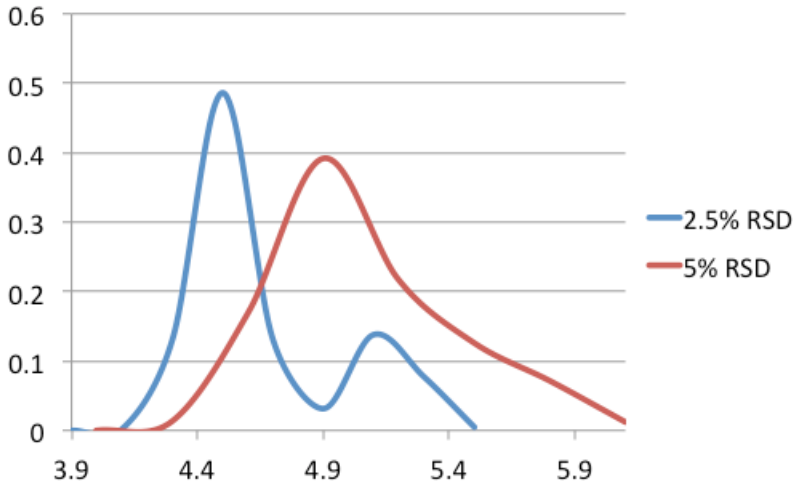
Sources of variance:

Fill Volume, Pressure Variation,

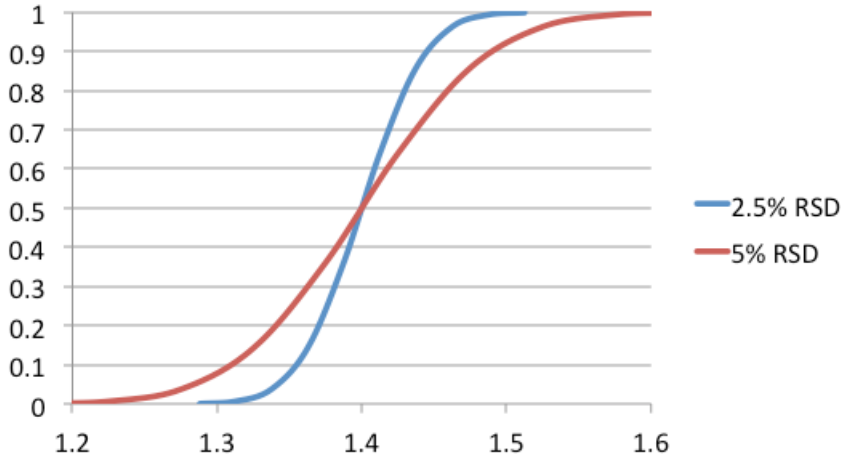
Product Resistance* (ice nucleation), Heat transfer Coefficient*

*** Major Contributor**

Vial Heat Transfer



Product Resistance

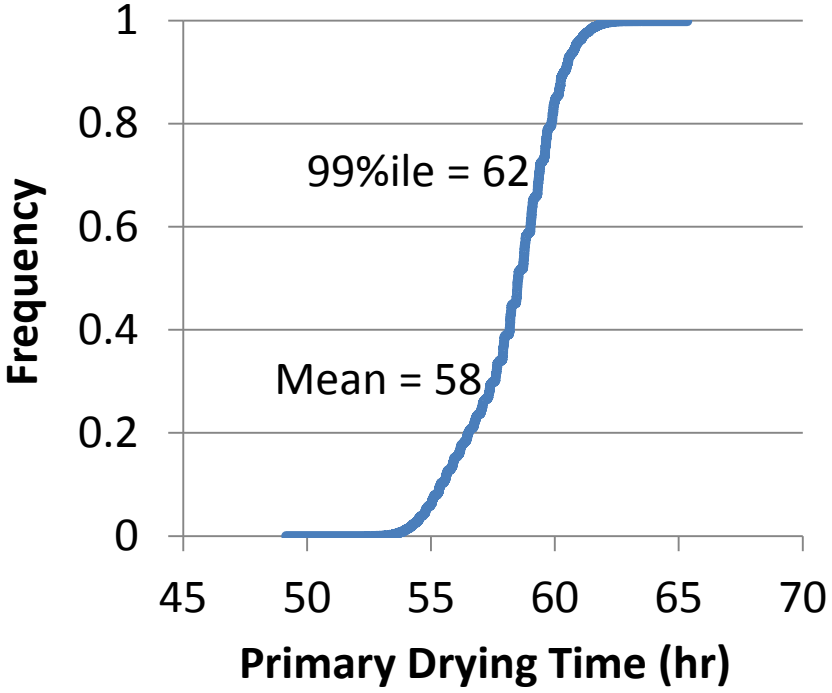


Note: 5% RSD more typical of most experimental systems

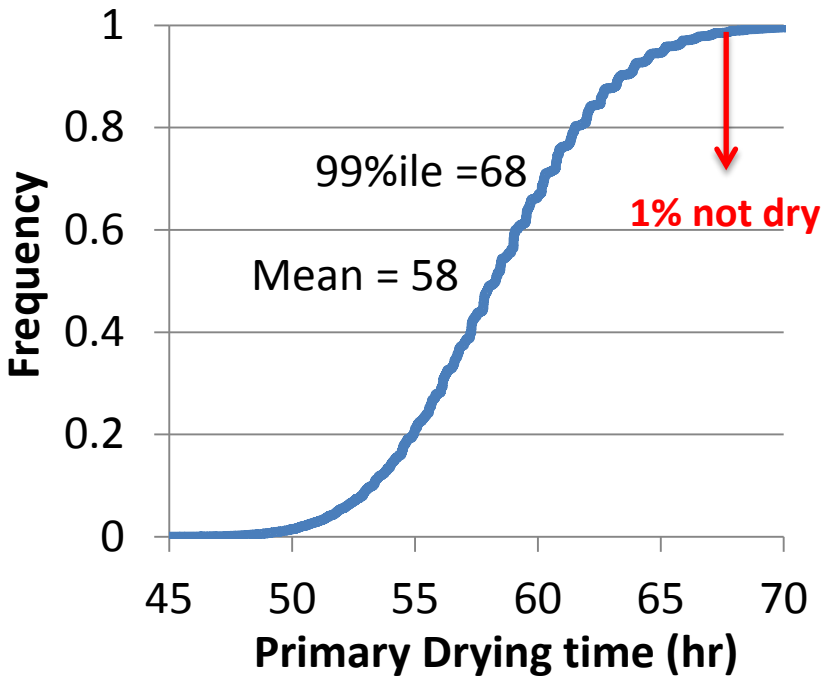
[#] **NIPTE-FDA Collaboration Projects**

Impact on Primary Drying Time

Low Variances (desirable)



High Variances (typical)

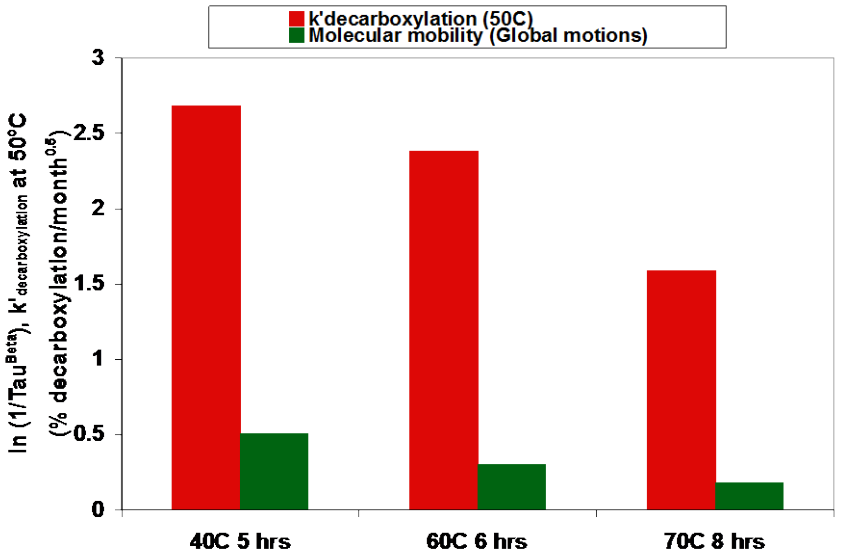


Solution: Minimize variance and need to adjust "Design Space" to accommodate expected variation

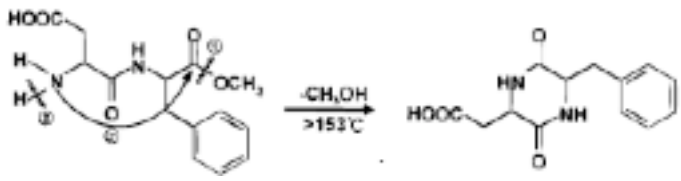
Product Temperature in Secondary Drying

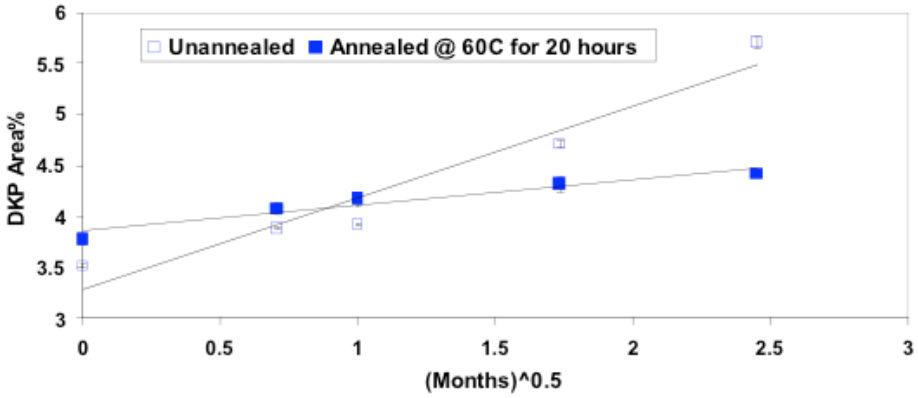
- **Exposure to high temperature Stabilizes!**

Decarboxylation in Moxalactam Na



Aspartame: sucrose (1:10) formulation





Water Contents are essentially Identical!

Conclusion: Secondary Drying Temperature matters

Conclusions

- **Formulation Matters**
- **Process Matters**
  - **Even if processes are “nominally” the same**
- **Intrinsic Variation in Process Matters**